Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents (Free Executive Summary) http://www.nap.edu/catalog/5825.html



### **Free Executive Summary**

### Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents

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<sup>&</sup>quot;...recommends development of more scientifically sound toxicity values for various nerve agents such as sarin, the poison gas used in the Tokyo subway terrorist attack." National Research Council

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### **Summary**

No reliable acute-exposure<sup>1</sup> standards have been established for the particular purpose of protecting soldiers from toxic exposures to chemical-warfare (CW) agents. Some human-toxicity estimates are available for the most common CW agents—organophosphorus nerve agents and vesicants; however, most of those estimates were developed for offensive purposes (that is, to kill or incapacitate the enemy) and were intended to be interim values only.

The U.S. Army's original purpose for developing human-toxicity estimates for CW agents was to enable it to predict the number of casualties that would occur during an offensive action in which the goal was to kill or incapacitate a certain fraction of the enemy forces (for example, killing or incapacitating a minimum of 50% of the least-sensitive (most-resistant) individuals). Such an approach would actually result in more than half of the exposed individuals dying (the "bonus effect"), because a certain percentage of those exposed would be expected to be more susceptible than the least-sensitive individual. Thus, exposure under the Army's original estimates would result in substantial "overkill." These estimates understate the toxicity of the agents and therefore are inappropriate for protecting soldiers.

<sup>&</sup>lt;sup>1</sup> A one-timeophwighte@nNatipoalinecademyantisciendelsr.All rights reserved. This executive summary plus thousands more available at http://www.nap.edu

Because of the possibility of a chemical attack by a foreign power, the Army's Office of the Surgeon General asked the Army's Chemical Defense Equipment Process Action Team (CDEPAT) to review the toxicity data for the nerve agents GA (tabun), GB (sarin), GD (soman), GF, and VX, and the vesicant agent sulfur mustard (HD) and to establish a set of exposure limits that would be useful in protecting soldiers from toxic exposures to those agents. In the 1994 report entitled *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier*, the team concluded that some of the existing human-toxicity estimates are too high and are inappropriate for use in protecting soldiers. In those cases, CDEPAT proposed new estimates for various routes of exposure—percutaneous vapor, vapor inhalation, and percutaneous liquid exposures. The proposed human-toxicity estimates are only for healthy

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Before making a decision on acceptance of the human-toxicity estimates proposed by CDEPAT, the Department of the Army requested that the National Research Council (NRC) independently review the CDEPAT report to determine the scientific validity of the proposed estimates. The NRC assigned this project to the Committee on Toxicology (COT) of the Board on Environmental Studies and Toxicology. The COT convened the Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents, which prepared this report. Members of the subcommittee were selected for their recognized expertise in the fields of toxicology, medicine, pathology, biostatistics, and risk assessment. The subcommittee was charged to review the Army's proposed human-toxicity estimates for GA, GB, GD, GF, VX, and HD. Specifically, the subcommittee was charged with the following tasks:

male military personnel. They must not be used for civilians.

- 1. Review the scientific protocols and quality of the toxicity data used in revising the human-toxicity estimates for acute exposures.
- 2. Review the toxicity estimates for mild and nonsevere effects and for severe and lethal effects.
- 3. Review the methods used in deriving the human-toxicity estimates for acute exposures.
- 4. Determine the appropriateness of the assumptions made in deriving the human-toxicity estimates for acute exposures.

The subcommittee was not asked to recommend new toxicity estimates

or to address the policy or operational consequences of lowering the proposed human-toxicity estimates. The subcommittee's evaluations of CDEPAT's proposed estimates for GA, GB, GD, GF, VX, and HD are summarized in Tables I through 6.

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The subcommittee's conclusions concerning the scientific validity of the proposed CDEPAT estimates are grouped in four categories: (1) some estimates were judged to be scientifically valid; (2) other estimates were judged adequate to serve as interim estimates until further research is conducted; (3) some estimates need to be lowered; and (4) a few estimates need to be raised.

The toxicity data that CDEPAT used to derive its proposed estimates were generated primarily from a data base developed from the 1930s to the 1960s. The existing human-toxicity estimates were based on experiments performed 30-40 years ago using various animal species in often poorly controlled studies with vastly different protocols. In reviewing the available toxicity data for the six CW agents, the subcommittee recognized that the quality of the relevant toxicity data is marginal, but it also recognized that the Army needs "best estimates" to protect its troops from exposure. For each chemical agent, data were available for only a few adverse health effects, such as death, incapacitation, cholinesterase (ChE) inhibition, miosis (a decrease in pupil size), and rhinorrhea (running nose), vesication, and erythema. Thus, even though the subcommittee concluded that some of CDEPAT's proposed estimates are scientifically valid, those conclusions are based on a limited toxicity data base. By current standards of toxicology, the toxicity data base for the agents is inadequate, and such inadequacy is a major obstacle to the Army in developing human-toxicity estimates with statistical confidence and in developing risk-management strategies.

The subcommittee recommends that the Army convene an expert panel to develop a research strategy for deriving more scientifically sound toxicity values for the agents of concern. The panel should first consider the use of such techniques as structure-activity relationships, the uncertainty factors, and in vitro systems for estimating human-toxicity values for CW agents.

If these approaches do not appear to be useful, animal and human experimentation may be recommended. Although additional research is clearly desirable to provide improved confidence in existing data, such research should not be performed on laboratory animals until expert judgment documents the need on a case-by-case basis. It must be documented that the data to be obtained from laboratory animals is needed to make a significant improvement in the protection of human health.

TABLE 1 Evaluation of Human-Toxicity for GA

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		я	route, that GA is ble but mmended ther research		udy that it assumption he stimate be stimate for LCt <sub>50</sub> ;	higher
	Rationale for Subcommittee's Evaluation	Proposed estimate supported by human data	Because of inadequate data on GA for this route, CDEPAT derived the estimate by assuming that GA is 0.5 times as toxic as GB; approach reasonable but estimate should be lowered because of recommended lowering of LCt <sub>50</sub> for GB for this route; further research recommended	ChE inhibition data used for proposing new recommendation	CDEPAT's proposed estimate based on a study that indicated the ratio of ICt <sub>50</sub> °/LC <sub>50</sub> is 0.75; that assumption used to establish ECt <sub>50</sub> . for severe effects; the subcommittee recommends that the ECt <sub>50</sub> estimate be lowered to correspond to the lowered estimate for LCt <sub>50</sub> ; further research recommended	Human data show that humans can tolerate higher exposures; further research recommended
	Subcommittee's Evaluation of Proposed Estimates for GA	Proposed estimate is scientifically valid	Proposed estimate should be lowered	Proposed estimate is scientifically valid	Proposed estimate should be lowered	Proposed estimate should be raised
city GA	CDEPAT's Proposed Estimates	15,000  mg- min/m <sup>3</sup>	70 mg-min/ m <sup>3</sup>	2,000 mg-	S0 mg-min/ m <sup>3</sup>	0.5 mg-min/ m <sup>3</sup>
Human-Toxicity Estimates for GA	Existing Estimates	20,000 mg- min/m <sup>3</sup>	135 mg- min/m³	None	None	0.9 mg- min/m <sup>3</sup>
	Route and Form of Exposure	Percutaneous, vapor	Inhalation, vapor	Percutaneous,		Inhalation, vapor
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		Estimates for GA	GA		
Saxagenty Saxage	Route and Form of Exposure	Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
°.	Percutaneous, liquid	1,500 mg for 70-kg man	1,500 mg for 70-kg man	Proposed estimate should be lowered	No uncertainty factors used in lieu of limited animal data for proposed estimate; further research recommended
P.C	Percutaneous, liquid	None	880 mg for 70-kg man	Proposed estimate should be lowered	In the absence of adequate human or animal data for this effect, CDEPAT established the estimate by assuming $ID_{50}^{\dagger}/LD_{50}$ ratio of 0.6 to estimate ED50; the subcommittee recommends that the ED <sub>50</sub> estimate be lowered to correspond to the lowered estimate for $LD_{50}$ ; further research recommended
ssarily a sarily a so: Liqui so: Liquid so: Liquid so: Liquid so: Liquid	or exposure that produce constant. Itaneous vapor exposure d dose causing lethality d dose causing a definer rexposure that produces dose causing incapacite	s lethality in 50% or inhalation va in 50% of the ex in effect in 50% of incapacitation in ation in 50% of the third of the incapacitation in the feet in 50% of the 50% of the feet in 50% of the feet in 50% of the feet in	% of the exposed anii por exposure causing posed animals. in 50% of the exposed he exposed populatio	nals. Ct refers to the product of cc g a defined effect (e.g., incapacitat ls. d population.	3 L October 2015 of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not a degessarily a constant.  9 Exposure that produces lethality in 50% of the exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).  10 Exposure that produces animals a defined effect in 50% of the exposed animals.  10 Exposure that produces incapacitation in 50% of the exposed population.  11 Exposure that produces incapacitation in 50% of the exposed population.  12 Exposure that produces incapacitation in 50% of the exposed population.  13 Exposure that produces incapacitation in 50% of the exposed population.  14 Exposure that produces incapacitation in 50% of the exposed population.  15 Exposure that produces incapacitation in 50% of the exposed population.  16 Exposure that produces incapacitation in 50% of the exposed population.  17 Exposure that produces incapacitation in 50% of the exposed population.  18 Exposure that produces incapacitation in 50% of the exposed population.

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TABLE 2 Evaluation of Human-Toxicity Estimates for GB

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		Rationale for Subcommittee's Evaluation	Proposed estimate supported by studies in monkeys and humans	Estimate too high because human studies show 100% lethality at 40 mg-min/m <sup>3</sup>	Estimate supported by studies of ChE inhibition in humans; further research recommended	ECt <sub>50</sub> /LCt <sub>50</sub> ratio of 0.7 used to develop estimate; LCt <sub>50</sub> for this route of exposure was lowered; therefore, ECt <sub>50</sub> should be lowered correspondingly; further research recommended	No effects in humans at 0.5 mg-min/m <sup>3</sup> ; effects begin to appear at $\approx 2$ mg-min/m <sup>3</sup> ; further research recommended	Estimate based on a ratio of ChE inhibition in rabbits and humans; however, human data concerning the relation between ChE inhibition and adverse effects are inconsistent; further research recommended
		Subcommittee's Evaluation of Proposed Estimates for GA	Proposed estimate is scientifically valid	Proposed estimate should be lowered	Proposed estimate is scientifically valid	Proposed estimate should be lowered	Proposed estimate should be raised	Low confidence in proposed estimate; proposed estimate should serve as interim value
es ioi on	ity GB	CDEPAT's Proposed Estimates	10,000 mg- min/m <sup>3</sup>	35 mg-min/ m <sup>3</sup>	1,200  mg- min/m <sup>3</sup>	25 mg-min/ m <sup>3</sup>	0.5 mg-min/ m <sup>3</sup>	1,700 mg for 70-kg man
LOAICHY ESUINAU	Human-Toxicity Estimates for GB	Existing Estimates	15,000 mg- min/m <sup>3</sup>	70 mg-min/ m <sup>3</sup>	None	35 mg-min/ m <sup>3</sup>	2 mg-min/ m <sup>3</sup>	1,700 mg for 70-kg man
PEDELE 2 EVALUATION OF FRUITAIN-LOAICHY ESUMMATES FOI OD		Route and Form of Exposure	Percutaneous, vapor	Inhalation, vapor	Percutaneous, vapor	Inhaiation, vapor	Inhalation, vapor	Percutaneous, liquid
IADLE 2 EVE	This	executive Solutions Solution Solutions Solutio	egnwu ohtiol aoo	National∰c nary plu <del>§</del> Yh	Schold Beshold	eg sz og szciences de more ava	Sill right Bill right Bill right	sÆeserved. n <del>ttp</del> ://www.nar

m-Toxicity ates for GB	ng CDEPAT's Subcommittee's Rationale for Subcommittee's Evaluation ates Proposed Evaluation of Proposed Estimates Estimates for GA	1,000 mg for Proposed estimate should In the absence of adequate data on GB for this effect, 70-kg man serve as interim value CDEPAT assumed that the ratio of $\mathrm{ID}_{50}$ ' $L_{50}$ is 0.6 and used that to estimate the $\mathrm{ED}_{50}$ values; further research recommended	Fig. 18 constant a constant as constant as a constant of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not an exposure that produces lethality in 50% of the exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects). Fig. 18 constant as a constant as a constant of the exposed animals.  Fig. 26. Liquid dose causing lethality in 50% of the exposed animals.  Fig. 26. Liquid dose causing incapacitation in 50% of the exposed population.  Fig. 26. Liquid dose causing incapacitation in 50% of the exposed population.  Fig. 27. Liquid dose causing incapacitation in 50% of the exposed population.  Fig. 27. Liquid dose causing incapacitation in 50% of the exposed population.  Fig. 27. Liquid dose causing incapacitation in 50% of the exposed population.
Human-Toxicity Estimates for GB	Existing CDEPAT's Estimates Proposed Estimates	None 1,000 mg for 70-kg man	ethality in 50% of the exposed an rinhalation vapor exposure causii 50% of the exposed animals. Iffect in 50% of the exposed animon in 50% of the exposed population
	Route and Form of Exposure	Percutaneous, liquid	apor exposure that produces I y a constant. ercutaneous vapor exposure o quid dose causing lethality in quid dose causing a defined e puid dose causing incapacitati
_	sexecty oo Secrity	pyrigh (@Nationa ltive symmary plu	ੇ ਜ਼ਿਲ੍ਹੇ ਹੈ ਹੈ ਹੈ ਮੈਂ ਨੂੰ ਲੈ ਲੈ ਲੈ ਲੈ ਜ਼ਿਲ੍ਹੇ Il Agage ਸ਼੍ਰੇਮ ਨੂੰ ਉਹ ਲੈ nces. All rights reserve us thousands more available at http://www

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should be lowered to correspond to the lowered estimate  for GB; further research recommended	Inhalation, 35 mg-min/ 25 mg-min/ Proposed estimate should vapor $m^3$ be lowered	Percutaneous, None 300 mg-min/ Proposed estimate should In the absence of adequate human or animal data, facts vapor m³ serve as an interim value proposed estimate based on assumption that GD is 4 times more toxic than GB for percutaneous exposure;	Percutaneous, None 2,500 mg- Proposed estimate is Proposed estimate based on assumption that GD is 4  min/m³ scientifically valid times more toxic than GB for percutaneous exposure  Samp-min/ Proposed estimate should GB are equipotent via this route; subcommittee recommends that LCt <sub>50</sub> estimate for GD be lowered to correspond to lowered estimate for GB; further research recommended	Roxicity Route and Form Existing CDEPAT's Subcommittee's Rationale for Subcommittee's Evaluation  System of Exposure Estimates Proposed Expinates Estimates Estimates for GA
ity Route and Form Existing CDEPAT's Subcommittee's of Exposure Estimates Proposed Evaluation of Proposed Estimates Of Exposure Estimates Proposed Evaluation of Proposed Estimates for GA Estimates for GA Estimates of Mone Minhm³ Scientifically valid Inhalation, 70 mg-min/ 35 mg-min/ Proposed estimate should be lowered be lowered as an interim value in m³ M³ M³ M³ M³ M²	Route and Form Existing CDEPAT's Subcommittee's of Exposure Estimates Proposed Evaluation of Proposed Estimates for GA Estimates None 2,500 mg-scientifically valid Inhalation, 70 mg-min/ 35 mg-min/ Proposed estimate is wapor m³ m³ be lowered be lowered bercutaneous, None 300 mg-min/ Proposed estimate should wapor m³ m³ serve as an interim value m³	Route and Form       Existing       CDEPAT's       Subcommittee's         of Exposure       Estimates       Proposed       Evaluation of Proposed         Percutaneous,       None       2,500 mg-       Proposed estimate is scientifically valid         Inhalation,       70 mg-min/       35 mg-min/       Proposed estimate should be lowered	ity Route and Form Existing CDEPAT's Subcommittee's of Exposure Estimates Proposed Evaluation of Proposed Estimates Estimates for GA	
Human-Toxicity Estimates for GD Route and Form Existing Of Exposure Estimates Proposed Estimates Estimates Estimates Froposed Estimates From CDEPAT's Estimates Estimates Estimates for GA Estimates None  2,500 mg-min/m³ scientifically valid Inhalation, m³ M³ M³ M³ M³ M³ Proposed estimate should be lowered be lowered serve as an interim value Inhalation, m³	Human-Toxicity Estimates for GD Route and Form Existing Of Exposure Estimates Proposed Estimates Estimates Estimates Froposed Estimates From CDEPAT's Estimates Estimates Estimates for GA Estimates From COA Estimates Estimates for GA Estimates From COA Estimates for GA Estimates	Human-Toxicity Estimates for GD Route and Form Existing CDEPAT's Subcommittee's Estimates Proposed Evaluation of Proposed Estimates For GA Exposure Estimates Proposed Estimates for GA Estimates None 2,500 mg-min/m³ scientifically valid min/m³ scientifically valid vapor m³ m³ m³ be lowered	Human-Toxicity Estimates for GD  ity Route and Form Existing CDEPAT's Subcommittee's of Exposure Estimates Proposed Evaluation of Proposed Estimates for GA	Human-Toxicity Estimates for GD

SUMM	ARY				
	Rationale for Subcommittee's Evaluation	In the absence of adequate human or animal data, proposed estimate based on assumption that GD is 2.5 times more potent than GB for miotic effects; subcommittee recommends that the LCt <sub>50</sub> estimate for GD be raised to correspond to the recommended raised estimate for GB; further research recommended	Percutaneous, 350 mg for 350 mg for Proposed estimate should Because of wide range of LD50 values in animals, or by Figure 1 animals, or by Figure 2 an interim value serve as an interim value subcommittee's confidence in the proposed estimate is low; CDEPAT's proposed estimate of 350 mg for 70-kg man should serve as an interim value; further research recommended recommended	In the absence of adequate human or animal data, proposed estimate was derived using the ID <sub>50</sub> e/LD <sub>50</sub> ratio of 0.6; the subcommittee recommends that CDEPAT's proposed estimate serve as an interim value; further research recommended	in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not ion vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects). the exposed animals. \$0% of the exposed animals. % of the exposed population.
	Subcommittee's Evaluation of Proposed Estimates for GA	Proposed estimate should be raised	Proposed estimate should serve as an interim value	Proposed estimate should serve as an interim value	nals. Ct refers to the product of cog a defined effect (e.g., incapacital s.
city	CDEPAT's Proposed Estimates	0.2 mg-min/ m <sup>3</sup>	350 mg for 70-kg man	200 mg for 70-kg man	in 50% of the exposed animation vapor exposure causing at the exposed animals. 50% of the exposed animals.
Human-Toxicity Estimates for GD	Existing Estimates	None	350 mg for 70-kg man	None	es lethality in 50% e or inhalation va in 50% of the ext de effect in 50% of the tation in 50% of tation in 50% of the 50% of the tation in 50% of the 50%
	Route and Form of Exposure	Inhalation, vapor	Percutaneous, liquid	Percutaneous, liquid	ELE 15. Vapor exposure that produces lethality flee assarily a constant.  ELD <sub>50</sub> : Percutaneous vapor exposure or inhala ELD <sub>50</sub> : Liquid dose causing lethality in 50% of EBD <sub>50</sub> . Liquid dose causing a defined effect in c ID <sub>50</sub> . Liquid dose causing incapacitation in 50
-	Sexection of the control of the cont	o <del>y</del> ignt © National tree summary plu	l ନ୍ଧିରିademy of Scieମି s-thousands more	ું ceકુ. સી rights re avealable at http:	And the state of t

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TABLE 4 Evaluation of Human-Toxicity Estimates for GF

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	"s Subcommittee's Rationale for Subcommittee's Evaluation  Evaluation of Proposed  Estimates for GA	<ul> <li>Proposed estimate should at ationale for the CDEPAT estimate not supported by serve as an interim value data; further research recommended</li> <li>In the absence of adequate data, proposed estimate based on assumption that GF, GD, and GB are equipotent; approach is reasonable; because LCt<sub>50</sub> for GB was recommended to be lowered, proposed value for GF should be lowered correspondingly; further research recommended</li> </ul>	nin/ Proposed estimate should Proposed estimate based on assumption that GF and GD serve as an interim value are equipotent; approach is reasonable; further research recommended	Proposed estimate should be lowered
ity 3F	CDEPAT's Proposed Estimates	2,500 mg- min/m <sup>3</sup> 35 mg-min/ m <sup>3</sup>	300 mg-min/ m <sup>3</sup>	25 mg-min/ m³
Human-Toxicity Estimates for GF	Existing Estimates	15,000 mg- min/m <sup>3</sup> None	None	None
	Route and Form of Exposure	Percutaneous, vapor Inhalation, vapor	Percutaneous, vapor	Inhalation, vapor
This	executive Secutive Secutive	ું grig © National Academy ર્ કર્માmmary plus thousands	gesterne FScHenges. Finotre atvaila	AF rights reserved.

Activity Route and Form Existing CDEPAT's Subcommittee's Rationale for Subcommittee's Evaluation of Proposed  Estimates Proposed Evaluation of Proposed  Estimates Proposed Evaluation of Proposed  Estimates For GA  Inhalation, None 0.2 mg-min/ Proposed estimate should In the absence of adequate human or animal data, the proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; because ECts, proposed value for GF should be raised correspondingly; further research recommended to be raised correspondingly; further research recommended to be raised and grant			Human-Toxicity Estimates for GF	city r GF		
Inhalation, None 0.2 mg-min/ Proposed estimate should be raised  Solution and the defects of a dequate human or animal data, the proposed estimate based on assumption that GF and G are equipotent; approach is reasonable; because ECt <sub>50</sub> for mild effects for GD was recommended to be raised proposed value for GF should be raised correspondingly; further research recommended in the absence of adequate human or animal data, the proposed estimate based on assumption that GF and G are equipotent; approach is reasonable; further research recommended are equipotent.	oxicity 7pe	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
Percutaneous, None 350 mg for Proposed estimate should In the absence of adequate human or animal data, proposed estimate based on assumption that GF and G 70-kg man serve as an interim value proposed estimate based on assumption that GF and G are equipotent; approach is reasonable; further research recommended.  None 200 mg for Proposed value should In the absence of adequate human or animal data, the proposed estimate based on assumption that GF and G 70-kg man serve as an interim value proposed estimate based on assumption that GF and G are equipotent; approach is reasonable; further research recommended are equipotent.	्र D <del>y</del> rigent © National	Inhalation, vapor	None	0.2 mg-min/ m <sup>3</sup>	Proposed estimate should be raised	In the absence of adequate human or animal data, the proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; because ECt <sub>50</sub> for mild effects for GD was recommended to be raised, proposed value for GF should be raised correspondingly; further research recommended
Percutaneous, None 200 mg for Proposed value should In the absence of adequate human or animal data, the fighers liquid 70-kg man serve as an interim value proposed estimate based on assumption that GF and G are equipotent; approach is reasonable; further research recommended	Açademy of Sci	Percutaneous, liquid	None	350 mg for 70-kg man	Proposed estimate should serve as an interim value	In the absence of adequate human or animal data, proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended
	egects Sil IIA segona	Percutaneous, Iiquid	None	200 mg for 70-kg man	Proposed value should serve as an interim value	In the absence of adequate human or animal data, the proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended

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TABLE 5 Evaluation of Human-Toxicity Estimates for V3

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TABLE 5 Eve	TABLE 5 Evaluation of Human-Toxicity Estimates for VX	Foxicity Estimate	es for VX		
This		Human-Toxicity Estimates for VX	ity VX		
executive	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
grif © Nat elummar	Percutaneous, vapor	None	150 mg-min/ m <sup>3</sup>	Proposed estimate should be considered an interim value	Degree of confidence in data is low to moderate; further research recommended
tional Acad y plus theu	Inhalation, vapor	30 mg-min/ m <sup>3</sup>	15 mg-min/ m <sup>3</sup>	Proposed estimate should be lowered	Degree of confidence in data is low to moderate; further research recommended
emayers But sects and sects	Percutaneous, vapor	None	10 mg-min/ m <sup>3</sup>	Proposed estimate should be considered an interim value	Degree of confidence in data is low; a no-observed-adverse-effect level (NOAEL) was not defined; further research recommended
e.e.e.e.e.e.e.e.e.e.e.e.e.e.e.e.e.e.e.	Percutaneous, vapor	None	25 mg-mill/ m <sup>3</sup>	Proposed estimate should be considered an interim value	Degree of confidence low to moderate; further research recommended
All rights r	Inhalation, vapor	25 mg-min/ m3	10 mg-min/ m3	Proposed estimate should be considered an interim value	Insufficient data; further research recommended
A A State of the cts	Inhalation, vapor	0.09 mg- min/m <sup>3</sup>	0.09 mg- min/m <sup>3</sup>	Proposed estimate is scientifically valid	Available human data support the proposed estimate
<sup>၁</sup> <sup>၇၄</sup> ဝှင် /. <del>n</del> ap.edu	Percutaneous, liquid	10 mg/70- kg man	5 mg/70-kg man	Proposed estimate should be lowered	Animal data indicate that the proposed estimate is too high; furthermore, no uncertainty factor used in lieu of variability associated with dermal penetration of various regions of body; further research recommended

Poxicity s for VX	CDEPAT's Subcommittee's Rationale for Subcommittee's Evaluation s Proposed Evaluation of Proposed Estimates Estimates for GA	kg 2.5 mg/70kg Proposed estimate should The ED <sub>50</sub> is based on the ID <sub>50</sub> °/LD <sub>50</sub> ratio; the man be lowered subcommittee recommends that the LD <sub>50</sub> be lowered, therefore, the ED <sub>50</sub> should be lowered correspondingly; further research recommended	Concentration (c) and exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not accessing a constant.  Program of the exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects).  Program of the exposed animals.
××	CDEPAT's S Proposed Estimates E	2.5 mg/70kg P man b	f the exposed animals rexposure causing a csed animals. The exposed animals exposed population.
Human-Toxicity Estimates for VX	Existing Estimates	5 mg/70-kg man	ces lethality in 50% of the or inhalation vaporty in 50% of the exposidation in 50% of the citation in 50% of the
	Route and Form of Exposure	Percutaneous, liquid	or exposure that produ constant. Itaneous vapor expost d dose causing lethali d dose causing incapac I dose causing incapac
-	sम्म oxicity o O	pyrighe©iNationa htive svimmary plu	ວັດ ກັບ ເຂົ້າການ ເຂົ້າ ເຂົ້າ ເຂົ້າ ເຂົາ ເຂົ້າ ເຂົາ ເຂົ້າ ເຂົ້າ ເຂົ້າ ເຂົ້າ ເຂົ້າ ເຂົ້າ ເຂົ້າ ເຂົ້າ ເຂົ້າ ເຂົ້າ ເຂົາ ເຂົ້າ ເຂົ້າ ເຂົ້າ ເຂົ້າ เຂົ້າ เຂົ້າ เล เข้ เข้ เข้ เข เข เข เข เข เข เข เข เข เข เข เข เข

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TABLE 6 Evaluation of Human-Toxicity Estimates for HD

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		Human-Toxicit HD	nan-Toxicity Estimates for		
ity	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
B	Percutaneous, vapor	10,000 mg min/m³	5,000 mg- min/m <sup>3</sup>	Proposed estimate should be lowered	Estimate might be too high because data from the most-sensitive species (rats and mice) not used; further research recommended
Ф	Inhalation, vapor	1,500 mg min/m <sup>3</sup>	900 mg-min/ m <sup>3</sup>	Proposed estimate is scientifically valid	CDEPAT averaged LCt <sup>50</sup> data in several animal species; in the absence of data on humans, that approach is reasonable
shold s.s	Percutaneous, vapor	None	50 mg-min/ m³ (moderate temperature); 25 mg-min/ m³ (hot temperature)	Proposed estimates should serve as interim values	In the absence of details on studies on which estimates were based, proposed estimate should be considered interim value; further research recommended
rights reserved.	Percutaneous, vapor	2,000 mg-min/ m³ (moderate temperature) 1,000 mg min/ m³ (hot temperature)	500 mg-min/ m³ (moderate temperature); <200 mg- min/m³ (hot temperature)	Proposed estimates are scientifically valid	Estimates based on human studies

			E de de	Subcommittee's Evaluation of Proposed	Rationale for Subcommittee's Evaluation
Sexective Co	Route and Form of Exposure	Existing Estimates	CDEPATS Proposed Estimates	Estimates for GA	
ovright 🙉	Inhalation, vapor	200 mg-min/ m <sup>3</sup> (moderate temperature)	100 Mg-Min/ m <sup>3</sup> moderate temperature)	Proposed estimate is scientifically valid	Proposed estimate supported by human data
sects	Inhalation, vapor	>50  mg min/ m <sup>3</sup>	$25 \text{ mg-min/}$ $\text{m}^3$	Proposed estimate is scientifically valid	Proposed estimate supported by human data
al'Aradam	Percutaneous, liquid	7,000 mg for 70-kg man	1,400 mg for 70kg man	Proposed estimate is scientifically valid	Proposed estimate supported by a study in dogs
by Schools Williams	Percutaneous, liquid	None	610 mg for 70-kg man	Proposed estimate is scientifically valid; however, it should be rounded to 600 mg for a 70-kg man to avoid appearance of precision that is not there	Proposed estimate is Proposed estimate by human data  2 febre

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SUMMARY 16

The experimental designs should include the following:

- Define if and when experiments with humans are appropriate.
- In the absence of human experimentation, define the most appropriate animal model for each specific toxicity value and agent, including the end points to be observed.
- Define the adequacy of the design in determining the toxicity values for healthy female as well as healthy male military personnel.
- Define the requirements for observation of reversibility of adverse health effects.
- Identify adverse health effects at the low end of the dose-response curve to determine threshold exposure levels.
- Identify confidence limits for the proposed estimates as a measure of the uncertainty of the estimated incidence of toxic effects.
- Identify potentiation or antagonistic effects from exposures to mixtures of chemical agents.
- Identify more-sensitive biological markers of exposure and effects for CW agents.

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## Review of Acute Human-Toxicity Estimates for Selected ChemicalWarfare Agents

Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents

Committee on Toxicology
Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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### **Preface**

Due to the Existence of large stocks of chemical-warfare (CW) agents, their easy producibility from ordinary industrial chemicals, and their potential lethal effects, there is a critical need to determine as precisely as possible the exposure levels at which CW agents cause toxic effects. This information could aid in protecting soldiers in the event of a CW attack.

This report, by the Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents of the National Research Council's Committee on Toxicology, is intended to assist the U.S. Army by assessing the scientific validity of existing human-toxicity estimates for several CW agents. The estimates considered in this report were proposed recently in the Army's Chemical Defense Equipment Process Action Team (CDEPAT) report entitled *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier* (1994). The report was authored by S.A. Reutter, Ph.D., and W.A. Wade, D.V.M.; it is classified "secret" and can be obtained only with permission from the director of the U.S. Army Edgewood Research, Engineering and Development Center, Edgewood, Md.

We gratefully acknowledge Carl Curling, Jerry Glasow, William

PREFACE

Klenke, Francis O'Donnell, Forrest Oliverson, Gerald Palmer, Sharon Reutter, Harry Salem, and Sandra Thomson (all from the U.S. Army) for providing background information. We also thank Gail Charnley (Commission on Risk Assessment and Risk Management) and Annetta Watson (Oak Ridge National Laboratory) for making presentations to the subcommittee and providing useful information.

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We are grateful for the assistance of the National Research Council staff in preparing this report. Staff members who contributed to this effort are Paul Gilman, executive director of the Commission on Life Sciences; James J. Reisa, director of the Board on Environmental Studies and Toxicology; Carol A. Maczka, program director for toxicology and risk assessment; Ruth E. Crossgrove, editor; Lucy V. Fusco, project assistant, and Catherine M. Kubik, senior program assistant. We especially wish to recognize the major contributions of the project director, Kulbir S. Bakshi, who directed the preparation of the subcommittee's report. His knowledge of the scientific and technical literature and his tireless efforts to obtain information and to organize the study plan, the subcommittee meetings, and the subcommittee's report aided in the successful completion of the project.

Finally, we would like to thank all the members of the subcommittee for their dedicated efforts throughout the development of this report.

LOREN D. KOLLER, PH.D.

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FOR SELECTED NERVE AND VESICANT AGENTS
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### 1—

### Introduction and Background

The U.S. Army's Chemical Defense Equipment Process Action Team (CDEPAT) recently conducted an extensive review of the scientific basis for toxicity estimates in use by the Army for several chemical-warfare (CW) agents: GA, GB, GD, GF, VX, and HD. Following a detailed analysis of the toxicity of these agents and using contemporary methods of analysis, CDEPAT concluded that many of the human-toxicity estimates in use would not protect the soldier adequately (CDEPAT 1994). Recalculations of the potencies of several of the CW agents indicate that their potencies are greater than previously determined. As a result, lower exposure levels of CW agents are expected to elicit adverse effects.

Before deciding whether to implement CDEPAT's recommendations, the U.S. Department of the Army requested that the National Research Council (NRC) independently review the CDEPAT report entitled *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates for Defending the Soldier*. The NRC assigned the project to the Committee on Toxicology (COT) of the Board on Environmental Studies and Toxicology. The COT convened the Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents, which conducted the study and prepared this report. Subcommittee members were chosen for their expertise in several specialties, including

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toxicology, medicine, pathology, biostatistics, and risk assessment. The subcommittee was charged with determining the scientific validity of CDEPAT's proposed human-toxicity estimates for CW agents for various routes of exposure (that is, percutaneous vapor exposures, vapor inhalation exposures, and percutaneous liquid exposures). The report considers only acute <sup>1</sup> exposures and acute effects. It should be noted that the human-toxicity estimates for the CW agents were proposed for healthy adult male soldiers only. They must *not* be used for the general population. Specifically, the subcommittee was charged with the following tasks:

- 1. Review the scientific protocols and the quality of the toxicity data used in revising the human-toxicity estimates for acute exposures.
- 2. Review the toxicity estimates for mild and nonsevere effects and for severe and lethal effects.
- Review the procedures used in deriving the human-toxicity estimates for acute exposures.
- 4. Determine the appropriateness of the assumptions made in deriving the human-toxicity estimates for acute exposures.

In reviewing the toxicity data and the proposed human-toxicity estimates for acute exposures, the subcommittee evaluated the quality of the data, the appropriateness of the procedures used in obtaining the estimates, and the assumptions made in deriving them. The subcommittee also determined whether the supporting documentation justified the proposed recommendations and whether the studies and toxicity end points were appropriate for deriving the toxicity estimates. In reviewing the proposed human-toxicity estimates, the subcommittee reviewed only the toxicity information presented in the CDEPAT report. It did not perform an independent literature search, nor did it review any data other than those presented in the report. In addition, the subcommittee was not asked to recommend new estimates or to address the policy or operational consequences of the proposed lower human-toxicity estimates.

The exposures used in the estimates are defined as follows:

• LCt<sub>50</sub> is the exposure to a vapor causing lethality in 50% of a given population and is expressed as the product of air concentration (c), in

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